



Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203



701027B

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT STAT
1	5,362,755	283	525		08/163,581	11/08/94	12/07/93	04 YES PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	SPC8905

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

** U.S. GPO: 1998-202-000/07120

**Chronology of Significant Activities Regarding IND 47,363 and NDA 20-837 for
Xopenex™ (levalbuterol HCl) Inhalation Solution O.P.C.**

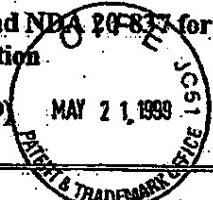
(February 28, 1995, through March 25, 1999)

MAY 21 1999

Date	Activity
February 28, 1995	IND - Original IND Submission
March 28, 1995	IND - Response to FDA Request of 3-27-95: Plasma sampling info in 28 d & 90 d oral & inhalation tox studies.
May 21, 1995	IND - Protocol Amendment: New Investigator to Protocol 051.005.0
October 9, 1995	IND - FDA Minutes of 7-25-95 Meeting. Protocol Amendment: Change in Investigator for study 051-005 - Atlanta site
January 29, 1996	IND - Information Amendment: Pharm/Tox (2 reports)
February 15, 1996	IND - EOP2 Package, Revised Investigator's Brochure dated 2-17-95, Clinical Info, Draft Labeling, New Protocol 051-012, Request for End of Phase 2 Meeting
March 13, 1996	IND - Response to FDA's requests for Draft Dog Inhalation Protocols
March 22, 1996	IND - Response to FDA Request of 3-19-96 for Information: Amendment to Chemistry, Manufacturing & Controls Section of IND—new method of manufacture of drug substance; new manufacturer & updated documentation for (R)-Albuterol and (RS)-Albuterol .024% & .042% (w-w)
April 12, 1996	IND - Revised draft of Protocol 051-012 in response to FDA's request of 4-10-96
May 31, 1996	IND - Sepracor Minutes for EOP2 Meeting held 4-25-96
June 5, 1996	IND - IND Annual Report (March 25, 1995 - March 27, 1996)
June 10, 1996	IND - Protocol Amendment: New Protocol (051-006), CMC Amendment (S)- Albuterol
July 1, 1996	IND - Protocol Amendment: New Protocol (051-024); Information Amendment: CMC for active comparator, (RS)-Albuterol Inhalation Solution; Contract Research Organization (PPD's) Responsibilities for 051-024 as item number 13 of Form 1571.
July 8, 1996	IND - Protocol Amendment: Change in Protocol (051-024, Amendment No. 1)
July 9, 1996	IND - Protocol Amendment: Change in Protocol (051-006, Amendment No. 1)
July 11, 1996	IND - Information Amendment: CMC. Responses to (a) questions from 5-3-95 letter from FDA and (b) questions raised during EOP2 Meeting from Fax 7-1-96.
July 23, 1996	IND - Protocol Amendment: Change in Protocol (051-006, Amendment No. 2)
July 29, 1996	IND - Protocol Amendment: New Protocol (051-025); Response to the Division's Fax of July 1, 1996.
July 31, 1996	IND - Protocol Amendment: New Protocol - Draft Pediatric Protocol (051-010) for FDA review
August 6, 1996	IND - FDA Minutes of CDER Office of Pharmaceutical Science-Sepracor Inc. Pharmaceuticals Meeting on August 6, 1996.
August 12, 1996	IND - IND Safety Report (051-006) - chest pain-pleurisy of viral etiology
August 12, 1996	IND - IND Safety Report (051-024) - exacerbation of asthma
August 20, 1996	IND - Protocol Amendment: New Investigators: Protocol 051-024
August 27, 1996	IND - Draft protocol 051-021 for FDA review

**Chronology of Significant Activities Regarding IND 47,363 and NDA 20-837 for
Xopenex™ (levalbuterol HCl) Inhalation Solution**

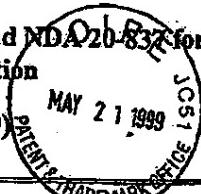
(February 28, 1995, through March 25, 1999) MAY 21, 1999



Date	Activity
September 12, 1996	IND - IND Safety Report, Protocol 051-024, left face numbness, Dr. Tommy C. Sim, Texas
September 20, 1996	IND - Protocol Amendment: New Investigators to Protocol 051-024
October 18, 1996	IND - Protocol Amendment: New Investigators to Protocol 051-024
October 28, 1996	IND - Information Amendment: CMC - lower dosage (0.156-0-312). Protocol Amendment: New Protocol (051-010).
November 4, 1996	IND - Protocol Amendment: Change in Protocol (Amendment No. 2 to 051-024)
November 11, 1996	IND - Protocol Amendment: Change in Protocol (Amendment No. 1 to 051-010)
November 18, 1996	IND - Protocol Amendment: New Investigator I. Fink, Milwaukee) to protocol 051-024
November 19, 1996	IND - Protocol Amendment: Change in Protocol (Final amendment to protocol 051-021)
December 16, 1996	IND - Protocol Amendment: New Investigators (R. Cohen, Lawrenceville, GA and S. Gawchik, Chester, PA) to protocol 051-024
December 23, 1996	IND - Protocol Amendment: Change in Protocol (Amendment No. 2 to Protocol 051-021)
December 24, 1996	IND - Safety Report: Exacerbation of Asthma (ADR#961116.0051.1)
December 24, 1996	IND - Safety Report: Exacerbation of Asthma (ADR#961114.0051.1)
January 8, 1997	IND - Protocol Amendment: Change in Protocol (Amendment No. 3 to protocol 051-021)
January 9, 1997	IND - Protocol Amendment: Additional new principal investigator (T Sim, Friendswood, TX) for 051-010
January 15, 1997	IND - Protocol Amendment: New Protocol (051-017) - Exercise Induced Protocol
January 27, 1997	IND - Request for Pre-NDA meeting
January 28, 1997	IND - Safety Report: Exacerbation of Asthma (ADR#970103.0051.1)
February 4, 1997	IND - Request to consider Study 051-006 as an adequate cumulative dose safety study
February 20, 1997	IND - USAN for (R)-albuterol HCl
February 20, 1997	IND - Pre-NDA Meeting Package
March 12, 1997	IND - Information Amendment: Pharm-tox
March 12, 1997	IND - Pre-NDA Meeting Package Supplement
March 20, 1997	IND - Response to FDA Request for information for Pre-NDA meeting
March 31, 1997	IND - General Correspondence: Request for tradename review
April 15, 1997	IND - Response to FDA Request for Information of 4-15-97: explanation for Levalbuterol NDA as a 505(b)(2)
April 16, 1997	IND - Safety Report: Death (SAE # 970324.0051.1)
May 7, 1997	IND - Protocol Amendment: Change in Protocol 051-017 (Amendments 1 & 2); Response to FDA's Request for Information in Fax dated 4-2-97

**Chronology of Significant Activities Regarding IND 47,363 and NDA 20-834 for
Xopenex™ (levalbuterol HCl) Inhalation Solution**

(February 28, 1995, through March 25, 1999)



Date	Activity
May 13, 1997	IND - Protocol Amendment: Changes in Forms FDA 1572 for Protocol No. 051-024
June 23, 1997	IND - General Correspondence: Confirm levalbuterol NDA as a 505(b)(2) application
June 30, 1997	NDA - Original NDA Submission
July 2, 1997	NDA - Submission: Type 1 DMF (Original Submission), Sepracor Canada Ltd.
July 11, 1997	IND - Protocol Amendment: Change in protocol (051-017 - Amendment No. 3 and revised Protocol #1)
July 17, 1997	NDA - Submission: Summary of proposed product for planned submission of Multidose Vial formulation
July 21, 1997	IND - General Correspondence: Re-submit Levalbuterol HCl Multidose Inhalation Solution Proposal and request for comments
July 22, 1997	IND - Protocol Amendment: New Protocol No. 051-023
July 24, 1997	IND - IND Annual Report (March 28, 1996 - June 30, 1997)
August 13, 1997	IND - Protocol Amendment: New Investigator (E. Israel, Boston) to 051-023
September 2, 1997	IND - Protocol Amendment: Change in Protocol (051-023 - Amendment No. 1)
September 4, 1997	NDA - Submission: 90-Day Conference Request
September 15, 1997	NDA - Submission: Clinical Site Inspection Packages for 051-024, Drs. Colton (FL), Edwards (NY), and Sim (TX)
September 17, 1997	NDA - Submission: Copies of PAI cover letters sent to Dr. Ju
October 13, 1997	NDA - Submission: Justification for the use of tradename, ZOPEN™
October 21, 1997	NDA - Submission: Responses to CMC comments dated August 13, 1997
October 31, 1997	NDA - Submission: Response to Request for Information: Clinical Documentation for Thomas Edwards, MD
November 4, 1997	NDA - Submission: Final internal audit report for Thomas Edwards, MD
November 4, 1997	NDA - Submission: Additional analysis of Study 051-024 requested by Dr. Nicklas on 10-31-97
November 6, 1997	NDA - Submission: Withdrawal of environmental assessment (V006, P001-032) and correspondence dated July 17, 1997
November 20, 1997	NDA - Submission: Section 9: 120-Day Safety Update
December 1, 1997	NDA - Submission: Study 051-010 body weight considerations
December 8, 1997	NDA - Submission: Request for tradename secondary evaluation
December 17, 1997	IND - Information Amendment: CMC
December 22, 1997	IND - Protocol Amendment: Change in Protocol (051-023 - Amendment No. 2)
December 23, 1997	IND - Protocol Amendment: New Protocol - 051-027 (Proposed Phase 4 Study)
January 12, 1998	NDA - Submission: Additional analysis of Study No. 051-024 Safety Data
January 21, 1998	NDA - Submission: Proposed tradename for levalbuterol, XOPEN
January 23, 1998	NDA - Submission: Request for tradename review-clarification

**Chronology of Significant Activities Regarding IND 47,363 and NDA 20-832 for
Xopenex™ (levalbuterol HCl) Inhalation Solution**

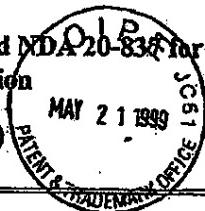
(February 28, 1995, through March 25, 1999)



Date	Activity
February 20, 1998	NDA – Submission: Clinical Site Inspection Package—Data for Howard Schwartz, MD (OH)
March 11, 1998	NDA – Letter to FDA: Request for tradename secondary LNC evaluation XOPEN™ for Levalbuterol HCl
March 17, 1998	IND – Protocol Amendment: Change in Protocol (Amendments to 051-027)
April 9, 1998	NDA – Amendment: Submission of Additional Analysis of Study 051-024, safety data
April 10, 1998	IND – Protocol Amendment: Change in Protocol (051-027)
May 13, 1998	NDA – Clarifications/response to CPT's 483s concerning the Levalbuterol NDA stability data/proposal for follow-up
May 18, 1998	IND – Protocol Amendment: New Investigators (051-027)
May 28, 1998	NDA – Submission: CMC Amendment: Responses to May 4 and 20, 1998 IR letters and May 26, 1998, Stability Updates Amendment
June 16, 1998	NDA – Letter to FDA: Amendment to NDA: Patent Information, U.S. Patent No. 5,760,090
June 18, 1998	IND – Protocol Amendment: New Investigators (051-027)
June 26, 1998	NDA – Submission: CMC Amendment – Remove Cipla as supplier of raw materials
July 1, 1998	NDA – Letter from FDA: Approvable Letter and Patient Labeling
July 10, 1998	NDA – Letter to FDA: Response to 7-1-98 Approvable Letter
July 20, 1998	NDA – Submission: Updated Questions for 7-21-98 Teleconference
July 23, 1998	IND – Protocol Amendment: New Investigators (051-027)
August 6, 1998	NDA – Resubmission and Complete Response to Regulatory Action Letter of 1 July 1998
September 18, 1998	IND – Protocol Amendment: New Investigator (051-027)
September 24, 1998	NDA – Submission: Response to FDA Communication of 31 August 1998
September 25, 1998	IND – Protocol Amendment: New Protocol (051-902 [CEP study])
September 30, 1998	NDA – Submission: Correction of albuterol aldehyde specification
October 19, 1998	NDA – Submission: Request for teleconference to discuss recalculating PDUFA goal date of March 25, 1999 (as described in FDA letter of 10-7-98) to February 11, 1999 (as described in Sepracor fax of 10-16-98) and to discuss final labeling.
October 22, 1998	IND – Protocol Amendment: New Investigators (051-902 [CEP study])
November 10, 1998	IND – Letter of Authorization to Incorporate by Reference, for IND 51,117/William Spiegel, MD
November 19, 1998	IND – Protocol Amendment: New Investigators (051-902 [CEP study])
December 2, 1998	IND – Protocol Amendments: Change in Protocol (051-027), New Investigators
December 2, 1998	IND – Annual Report (July 1, 1997 – June 30, 1998)
December 11, 1998	NDA – Submission: Issuance of U.S. Patent No. 5,844,002

**Chronology of Significant Activities Regarding IND 47,363 and NDA 20-837 for
Xopenex™ (levabuterol HCl) Inhalation Solution**

(February 28, 1995, through March 25, 1999)



Date	Activity
December 18, 1998	NDA – Submission: Response to FDA request for diskettes containing CMC information from August 6, 1998; September 24 and 30, 1998 (2 diskettes and accompanying letter).
December 23, 1998	IND – Protocol Amendment: New Investigators (051-902 [CEP Study])
December 24, 1998	IND – Protocol Amendment: New Investigators (051-027)
January 8, 1999	NDA – Submission: Response to request (of 1-4-99) for electronic copy of CMC data in the 5-28-98 submission
January 28, 1999	NDA – Submission: Information on Stability Testing—discontinuance of Consumer Product Testing Co. for stability testing of drug substance and drug product
January 29, 1999	NDA – Submission: Electronic Copy of 1-28-99 Submission—Information on Stability Testing
February 16, 1999	IND – Protocol Amendment: New Principal Investigator, 051-027 (Peter Economou, MD, Albuquerque)
February 24, 1999	NDA – Submission: Acknowledgement of the fax of revised draft labeling received 2-23-99. Reference made to submissions of 8-6-98 and 9-24-98.
March 8, 1999	NDA – Submission: Revised Draft Labeling, Version 03-08-99
March 10, 1999	NDA – Submission: Proposed Core Promotional Materials
March 15, 1999	IND – Information Amendment: Pharmacology/ Toxicology (Document Nos. 051-820, 051-821, 051-486, 051-463, 051-476, and 051-465A)
March 18, 1999	NDA – Submission: Response to FDA Communication Dated 15 March 1999 (CMC Comments)—includes updated stability data for the drug substance and drug product at the 24-month time interval
March 18, 1999	NDA – Submission: Samples of cartons and foil pouch labels to replace those previously submitted on 24 September 1998, including foil-pouch for the 0.63 mg/3mL vials, which changed since the September submission
March 22, 1999	NDA – Submission: Safety Update and CMC Information (provides information requested during teleconferences of March 16 and March 19, 1999)
March 23, 1999	NDA – Submission: Revised Draft Labeling, Version 03-23-99 (requested during teleconference of March 22, 1999).
March 24, 1999	NDA – Submission: Commitment regarding package labeling (foil pouches)
March 25, 1999	IND – Protocol Amendment: Protocol Concept—Submission of proposal to conduct pediatric study 051-031
March 25, 1999	NDA – FDA Approval Letter for NDA 20-837



BOX PATENT EXT.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, et al.

Assignee: Sepracor, Inc..

Issue Date: November 8, 1994

CERTIFICATION

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

I, Harold C. Wegner, do hereby certify that this accompanying application for extension of the term of U.S. Patent 5,362,755 under 35 U.S.C. § 156, including its attachments and supporting papers is being submitted as one original and one duplicate copy thereof.

Respectfully submitted,

21 May 1999
Date

H.C. Wegner
for Harold C. Wegner
Reg. No. 25,258

Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, D.C. 20007-5109
Tel: 202-672-5300
Fax: 202-672-5399

BOX PATENT EXT.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

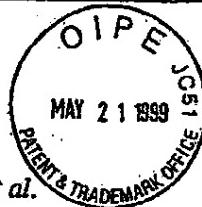
Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, et al.

Assignee: Sepracor, Inc.

Issue Date: November 8, 1994



DECLARATION

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

As agent for the owner of record of U.S. Patent 5,362,755 I declare that:

- (1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have general authority from the owner of United States Patent 5,362,755 to act on behalf of the owner in patent matters;
- (2) I have reviewed and understand the contents of the accompanying application, which is submitted pursuant to 37 C.F.R. § 1.740 for extension of U.S. Patent 5,362,755;
- (3) I believe that U.S. Patent 5,362,755 is subject to extension pursuant to 37 C.F.R. § 1.710;
- (4) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

BOX PATENT EXT.

(5) I believe that U.S. Patent 5,362,755, for which this extension is sought, meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,362,755.

Respectfully submitted,

21 May 1999
Date

H.C. Wegner
for Harold C. Wegner
Reg. No. 25,258

Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, D.C. 20007-5109
Tel: 202-672-5300
Fax: 202-672-5399

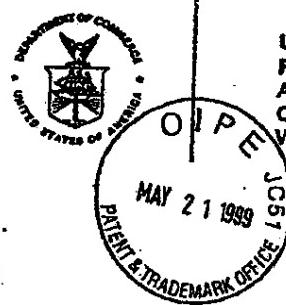


ATTACHMENT F

Letters

DLEV012325

JUL 10 1996



Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

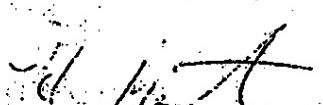
Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 4,309,445, which issued January 5, 1982, was filed on June 25, 1996, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, REDUX™ (dexfenfluramine hydrochloride), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use, and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of REDUX™ (dexfenfluramine hydrochloride) is considered to be the first permitted commercial use of the product. It is noted that the application argues that, although a racemate of REDUX™, fenfluramine (PONDIMIN®), has been previously approved, the prior approval of PONDIMIN® should not disqualify the approval of REDUX™ from being considered the first permitted commercial use of dexfenfluramine hydrochloride. See particularly Attachment E to the application for patent term extension.

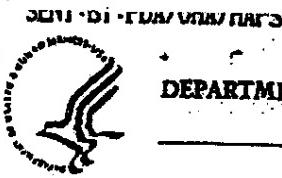
Inquiries regarding this communication should be directed to Karin Tyson at (703) 306-3159.


Hiram A. Bernstein
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Project

cc: Charles E. Van Horn
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

kt

DLEV012326



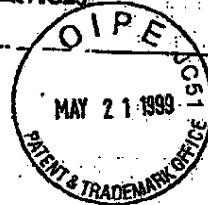
• 11-21-96 : 9:24 :

301 443 0232-

703 308 6916: # 2/2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857Re: REDUX™
Docket No. 96E-0265

NOV 2 | 1996

Stephen G. Kunin
 Deputy Assistant Commissioner for
 Patent Policy and Projects
 U.S. Patent and Trademark Office
 Box Pat Ext
 Assistant Commissioner for Patents
 Washington, D.C. 20231

Dear Mr. Kunin:

RECEIVED
 NOV 2 1996
PATENT & TRADEMARK OFFICE

This is in regard to the application for patent term extension for U.S. Patent No. 4,309,445 filed by Interneuron Pharmaceuticals, Inc. under 35 U.S.C. § 156. The human drug product claimed by the patent is REDUX™ (dexfenfluramine hydrochloride), which was assigned New Drug Application (NDA) No. 20-344.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of this product, as defined under 35 U.S.C. § 156(d)(1), and interpreted by the courts in *Globo Operations UK Ltd. v. Quigley*, 706 F. Supp. 1224 (E.D. Va. 1989), aff'd, 894 F.2d 392 (Fed. Cir. 1990).

The NDA was approved on April 29, 1996, which makes the submission of the patent term extension application on June 25, 1996, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A), we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely,

Ronald L. Wilson, Director
 Health Assessment Policy Staff
 Office of Health Affairs

cc: Charles E. Van Horn
 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP.
 1300 I Street, N.W.
 Washington, D.C. 20005-3315

DLEV012327



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JUL 29 1999

David T. Read
Acting Director, Regulatory Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

Dear Mr. Read:

The attached application for patent term extension of U.S. Patent No. 5,362,755 was filed on May 21, 1999, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, XOPONEX® (levalbuterol hydrochloride), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of XOPONEX® (levalbuterol hydrochloride) is considered the first permitted use of levalbuterol hydrochloride, or a salt or ester thereof. As noted in the application, albuterol has been previously approved and albuterol contains levalbuterol hydrochloride. See also the Prescription Drug Product List, Page 3-10, Approved Drug Products with Therapeutic Equivalence Evaluations, 18th Edition, attached. In addition, the posting on FDA's home page (<http://www.fda.gov/cder/da/da0399.HTM>) for the approval of XOPONEX indicates that the approval of levalbuterol hydrochloride the approval of a new formulation (a new dosageform or new formulation of an active ingredient already on the market) and not a new drug. See attachment 2.

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)308-6916 (facsimile).

Karin Tyson

Karin Tyson
Senior Legal Advisor/Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: HAROLD C. WEGNER
FOLEY & LARDNER
WASHINGTON HARBOUR, SUITE 500
3000 K STREET NW
WASHINGTON DC 20007-5109

Attachment #1

PRESCRIPTION DRUG PRODUCT LIST

3-10

ALBUTEROL

ALBENDAZOLE

TABLET; ORAL

ALBENZA

SMITHKLINE BEECHAM

200MG.

N2066 001

AB

JUN 11,

1996

AEROSOL, METERED/ INHALATION

MDDISOL

AB

NORTON WATERFORD

AB

0.09MG/INH

AB

DEC 28,

1995

N17559 001

AB

N19473 001

AB

DEC 28,

1995

N19243 002

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JAN 14,

1987

N19243 001

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JAN 14,

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N19243 002

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APR 23,

1992

N19269 002

AB

JAN 16,

1987

N19269 001

AB

JAN 16,

1987

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Attachment # 2

U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Drug Approvals for March 1999

Definitions and Notes

March 1999

Original New Drug Applications

Original Application #: 020966

Approval Date: 30-MAR-99

Trade Name: SPORANOX

Chemical Type: 3

Therapeutic Potential: S

Dosage Form: INJECTABLE

Applicant: JANSSEN RESEARCH FDN DIV JOHNSON AND JOHNSON

Active Ingredient(s): ITRACONAZOLE

OTC/RX Status: RX

Indication(s): For the treatment of blastomycosis, histoplasmosis and aspergillosis in immunocompromised and non-immunocompromised patients

Original Application #: 020908

Approval Date: 26-MAR-99

Trade Name: VAGIFEM

Chemical Type: 3

Therapeutic Potential: S

Dosage Form: TABLET

Applicant: NOVO NORDISK PHARMACEUTICAL INC

Active Ingredient(s): ESTRADIOLE

OTC/RX Status: RX

Indication(s): For the relief of postmenopausal atrophic vaginitis due to estrogen deficiency

Original Application #: 020837

Approval Date: 25-MAR-99

Trade Name: XOPENEX

Chemical Type: 3

Therapeutic Potential: S

Dosage Form: SOLUTION

Applicant: SEPRACOR PHARMACEUTICALS

Active Ingredient(s): LEVALBUTEROL HYDROCHLORIDE

OTC/RX Status: RX

Indication(s): For the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease

Original Application #: 020992

Approval Date: 24-MAR-99

Trade Name: CENESTIN

Chemical Type: 3

Therapeutic Potential: S

Dosage Form: TABLET

Applicant: DURAMED PHARMACEUTICALS INC

Active Ingredient(s): ESTROGENS, CONJUGATED

OTC/RX Status: RX

Indication(s): For use in the treatment of moderate-to-severe vasomotor symptoms associated with the menopause

Original Application #: 020612

Approval Date: 19-MAR-99

Trade Name: LIDODERM

Chemical Type: 3

Therapeutic Potential: S

Dosage Form: FILM, EXTENDED RELEASE

Applicant: HIND HEALTH CARE

Active Ingredient(s): LIDOCAINE

OTC/RX Status: RX

Indication(s): For the treatment of pain in post-herpetic neuralgia

Original Application #: 020980

Approval Date: 09-MAR-99

Trade Name: LAMISIL

Chemical Type: 6

Therapeutic Potential: S

Dosage Form: EMULSION, CREAM

Applicant: NOVARTIS PHARMACEUTICALS CORP

Active Ingredient(s): TERBINAFINE HYDROCHLORIDE

OTC/RX Status: OTC

Indication(s): For the treatment of tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm) due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*

Original Application #: 020994

JAN-06-2004 10:54

DIDP

DEPARTMENT OF HEALTH & HUMAN SERVICES

3018274576 P. 02/02
Public Health Service

Food and Drug Administration
Rockville MD 20857

Re: Xoponex
Docket No. 99E-5116

The Honorable James E. Rogan
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 2327
Arlington, VA 22202

DEC 30 2002

Dear Director Rogan:

This is in regard to the application for patent term extension for U.S. Patent No. 5,362,755 filed by Sepracor, Inc., under 35 U.S.C. § 156. The human drug product claimed by the patent is Xoponex (levalbuterol), which was assigned new drug application (NDA) No. 20-837.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989), *aff'd*, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on March 25, 1999, which makes the submission of the patent term extension application on May 21, 1999, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad
Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, NW
Washington, DC 20007-5109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH et al.

Assignee: Sepracer, Inc.

Issue Date: November 8, 1994

STATUS INQUIRY

FAX RECEIVED

Commissioner for Patents and Trademarks
Washington, D.C. 20231

APR 01 2003

PETITIONS OFFICE

Applicants respectfully inquire as to the status of the above-referenced patent term extension. The patent has an issue date of November 8, 1994. A Request for Extension of Patent Term Under 35 U.S.C. §156 was filed May 21, 1999. The last known communication regarding this patent was a letter dated December 30, 2002 (copy attached), to The Honorable James E. Rogan, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office from Jane A. Axelrad, Associate Director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration. To date, no further communication has been received on this application.

Respectfully submitted,

Date April 1, 2003

By Stephen B. Maebius

FOLEY & LARDNER,
Customer Number: 22428

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

22428

PATENT TRADEMARK OFFICE

Telephone: (202) 672-5569
Facsimile: (202) 672-5399

002.883485.1

DLEV012333

FOLEY & LARDNER
 ATTORNEYS AT LAW
 WASHINGTON HARBOUR
 3000 K STREET, N.W., SUITE 500
 WASHINGTON, D.C. 20007-5100
 TELEPHONE: (202) 672-5300
 FACSIMILE: (202) 672-5399

FACSIMILE TRANSMISSION

Total # of Pages 3 (including this page)

TO:	PHONE:	FAX #:
KARIN FERRITER U.S. Patent and Trademark Office Office of Petitions	703-306-3159	703-308-6916

From: Diana Meinecke, Legal Assistant to
 Stephen B. Maebius
 Sender's Direct Dial: 202-945-6135
 Date: April 1, 2003

FAX RECEIVED

APR 01 2003

PETITIONS OFFICE

MESSAGE:

U. S. Patent No. 5,362,755
 Sepracor, Inc.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741 in reference to the required Amendment fee.

[Signature]
 Stephen B. Maebius, Reg. No. 35,284

CERTIFICATION

I hereby certify that this document is being facsimile transmitted to U.S. Patent and Trademark Office, Attn: Karin Ferriter, Office of Petitions, on the date shown below. (1) Stans Inquiry.

4/1/03
 Date

Diana H. Meinecke
 Diana H. Meinecke

If there are any problems with this transmission or if you have not received all of the pages, please call 202-945-6135.

Operator:	Time Sent:	Return Original To:
		Diana Meinecke

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Cover Page 1 of 1

DLEV012334



03/27/03 17:04

DEPARTMENT OF HEALTH & HUMAN SERVICES

NO. 822 D82

Public Health Service

Food and Drug Administration
Rockville MD 20857Re: Xopenex
Docket No. 99E-5116

DEC 30 2003

FAX RECEIVED

APR 01 2003

The Honorable James R. Rogan
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 2327
Arlington, VA 22202

Dear Director Rogan:

This is in regard to the application for patent term extension for U.S. Patent No. 5,362,753 filed by Sepracor, Inc., under 35 U.S.C. § 156. The human drug product claimed by the patent is Xopenex (levalbuterol), which was assigned new drug application (NDA) No. 20-837.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Gilko Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989), aff'd, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on March 25, 1999, which makes the submission of the patent term extension application on May 21, 1999, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that this subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axstad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, NW
Washington, DC 20007-5109

CDR AVAILABLE COPY

DLEV012335



HESLIN ROTHENBERG FARLEY & MESITI P.C.

K COFC #42

PATENT & TRADEMARK OFFICE
ROSE E. Heslin
Jeff Rothenberg
Kevin P. Radigan
Susan E. Farley
Nicholas Mesiti
Philip E. Hansen*
Blanche E. Schiller
Wayne F. Reinke
Candice J. Clement
David P. Miranda

*Patent Agent

INTELLECTUAL PROPERTY LAW

PATENTS • TRADEMARKS • COPYRIGHTS

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David A. Pascarella
Victor A. Cardona
Lee Palmateer
John Pietrangelo*
Brett M. Hutton
James M. Syta
Martha L. Boden
Of Counsel

July 2, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate

JUL 14 2003

of Correction

Re: Correction of Mistake in Printed Patent
Under §1480 of the Manual of Patent
Examining Procedures

U.S. Patent No.: 5,362,755
Date of Patent: November 8, 1994
Inventor(s): Barberich et al.
Our File No.: 0701.027B

Dear Sir:

Upon proofreading the above-referenced patent, we noticed an error in the printed patent made by the Patent Office.

Transmitted herewith is a proposed Certificate of Correction effecting a corrective amendment.

The patentee respectfully solicits the granting of the requested Certificate of Correction.

Respectfully submitted,

Philip E. Hansen
Registration No. 32,700
Agent for Applicants

PEH/cma
Enclosure

NAUSERS\STAFF\CMA\Samples\0701027B-LET01-PTO.DOC
July 2, 2003

DLEV012336

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Claims:

Claim 6:

Col. 4, line 30, delete the word "or" and insert the word --of--

MAILING ADDRESS OF SENDER:

Philip E. Hansen, Ph.D.
Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

PATENT NO. : 5,362,755

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4.

Line 30, delete the word "or" and insert the word -- of --

Signed and Sealed this

Thirtieth Day of September, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

DLEV012338



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENT
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

MAILED

JAN 06 2004

REEXAM UNIT

Dear Mr. Read:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,362,755. The application was filed on May 21, 1999, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term restoration. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)872-9411 (facsimile).

Karin Ferriter
Karin Ferriter
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street NW
Washington DC 20007-5109

RE: XOPONEX @ (Levalbuterol HCl)
Docket No. 99E-5116



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Re: Xopenex
Docket No.: 99E-5116

JUN 23 2008
The Honorable Jon Dudas
Acting Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director Dudas:

This is in regard to the application for patent term extension for U.S. Patent No. 5,362,755, filed by Sepracor, Inc., under 35 U.S.C. section 156 *et seq.* We have reviewed the dates contained in the application and have determined the regulatory review period for Xopenex, the human drug product claimed by the patent.

The total length of the regulatory review period for Xopenex is 1,458 days. Of this time, 824 days occurred during the testing phase and 634 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: March 30, 1995.

The applicant claims February 28, 1995, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was March 30, 1995, which was thirty days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act: June 30, 1997.

FDA has verified the applicant's claim that the new drug application (NDA) for Xopenex (NDA 20-837) was initially submitted on June 30, 1997.

3. The date the application was approved: March 25, 1999.

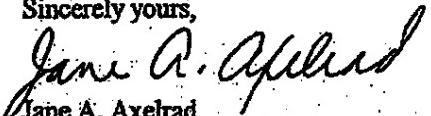
FDA has verified the applicant's claim that NDA 20-837 was approved on March 25, 1999.

Dudas - Xopenex - page 2

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, NW
Washington, DC 20007-5109



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Re: Xopenex
Docket No.: 99E-5116

The Honorable Jon Dudas
Acting Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director Dudas:

This is in regard to the application for patent term extension for U.S. Patent No. 5,362,755, filed by Sepracor, Inc., under 35 U.S.C. section 156 *et seq.* We have reviewed the dates contained in the application and have determined the regulatory review period for Xopenex, the human drug product claimed by the patent.

The total length of the regulatory review period for Xopenex is 1,458 days. Of this time, 824 days occurred during the testing phase and 634 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: March 30, 1995.

The applicant claims February 28, 1995, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was March 30, 1995, which was thirty days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act: June 30, 1997.

FDA has verified the applicant's claim that the new drug application (NDA) for Xopenex (NDA 20-837) was initially submitted on June 30, 1997.

3. The date the application was approved: March 25, 1999.

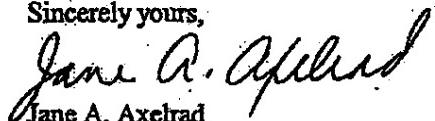
FDA has verified the applicant's claim that NDA 20-837 was approved on March 25, 1999.

Dudas - Xopenex - page 2

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,



Jane A. Axelrad

Associate Director for Policy
Center for Drug Evaluation and Research

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, NW
Washington, DC 20007-5109



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Re: Xopenex
Docket No. 99E-5116

The Honorable Jon Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 1450
Alexandria, VA 22313-1450

APR 8 2005

Dear Director Dudas:

This is in regard to the patent term extension application for U.S. Patent No. 5,362,755 filed by Sepracor, Inc. under 35 U.S.C. § 156. The patent claims Xopenex (levalbuterol), NDA 20-837.

In the July 12, 2004, issue of the Federal Register (69 Fed. Reg. 41812), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before January 10, 2005, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad
Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Harold C. Wegner
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, NW
Washington, DC 20007-5109

DLEV012344



UNITED STATES PATENT AND TRADEMARK OFFICE

OCT 11 2005

Commissioner for Patents
 United States Patent and Trademark Office
 P.O. Box 1450
 Alexandria, VA 22313-1450
www.uspto.gov

Harold C. Wegner
 Foley & Lardner
 Washington Harbour, Suite 500
 3000 K Street NW
 Washington DC 20007-5109

In Re: Patent Term Extension
 Application for
 U.S. Patent No. 5,362,755

A determination has been made that U.S. Patent No. 5,362,755, which claims the drug product XOPONEX (levabuterol HCl), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 503 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 503 days.

The period of extension has been calculated using the Food and Drug Administration (FDA) determination of the length of the regulatory review period published in the Federal Register of July 12, 2004 (69 Fed. Reg. 41812). Under 35 U.S.C. § 156(c):

$$\begin{aligned} \text{Period of Extension} &= \frac{1}{2} (\text{Testing Phase}) + \text{Approval Phase} \\ &= \frac{1}{2} (824 - 0) + 634 \\ &= 1,046 \text{ days} \end{aligned}$$

Since the regulatory review period began March 30, 1995, after the patent issue date (November 8, 1994), the entire period has been considered in the above determination. No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

However, the 14 year exception of 35 U.S.C. § 156(c)(3) operates to limit the term of the extension in the present situation because it provides that the period remaining in the term of the patent measured from the date of approval of the approved product plus any patent term extension cannot exceed fourteen years. The period of extension calculated above, 1,046 days, would extend the patent from November 8, 1994 (35 U.S.C. § 154) to September 19, 2014, which is beyond the 14-year limit (the approval date is March 25, 1999, thus the 14 year limit is March 25, 2013). The period of extension is thus limited to March 25, 2013, by operation of 35 U.S.C. § 156(c)(3). Accordingly, the period of extension is the number of days to extend the term of the patent from its original expiration date, November 8, 2011, to and including March 25, 2013, or 503 days.

The limitations of 35 U.S.C. § 156(g)(6) do not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	5,362,755
Granted:	November 8, 1994
Applicant:	Timothy J. Barberich, et al.

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Title: Method for Treating Asthma Using Optically Pure
(R)-Albuterol
Classification: 514/649
Product Trade Name: XOPONEX (levalbuterol HCl)
Term Extended: 503 days
Expiration of Extension: March 25, 2013

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RE: XOPONEX (levalbuterol HCl)
FDA Docket No.: 99E-5116

Attention: Claudia Grillo

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(56) Documents cited

EP-0455155 A1 WO 91/09596 A1
Chem. Pharm. Bull. 26(4), 1123-9 (1976)
J. Med. Chem. 14(9), 895-6 (1971)
J. Liq. Chromatogr. 11, 2147-63 (1988)
Biochem. Pharmacol. 35(12) 1981-5, (1986)
Br. J. Clin. Pharmacol. 27, 49-56, (1989)

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(54) Bronchodilator enantiomers.

(57) Improved use of selective B₂ sympathomimetic bronchodilator drugs in the therapy of obstructive or inflammatory airways disease, e.g. asthma, comprises use in enantiomeric rather than conventional racemic form. The improved use reduces occurrence of side effect, e.g. exacerbation of basal disease status or compromise or deterioration of lung function. The active compound is used in the form of its R-enantiomer e.g. Albuterol, Terbutaline, Fenoterol, Metaproterenol, Orciprenaline, Carbuterol or Isoetharine, optionally in combination with Ketotifen.

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IMPROVED USE OF β_2 BRONCHODILATOR DRUGS

The present invention relates to a new and improved use of selective β_2 sympathomimetic bronchodilator drugs in the therapy of obstructive or inflammatory airways disease, especially asthma.

Bronchodilator drugs employed in the therapy of obstructive or inflammatory airways disease, e.g. asthma, are divisible into three classes:

1. Adrenergic or sympathomimetic drugs (the terms "adrenergic" and "sympathomimetic" are used in the art interchangeably);
2. Anticholinergic drugs; and
3. Methylxanthine drugs.

The present invention is concerned with the first of these drug classes.

The adrenergic or sympathomimetic drugs are so called because they are understood to exert their effect through their action on the body's adrenergic receptors of which there are three functionally divided types, the α , β_1 and β_2 receptors. On the basis of their interaction with these three receptor types, the adrenergic or sympathomimetic drugs are in turn classifiable into three groups:

- 1.1 Non-selective sympathomimetic drugs;
- 1.2 Non-selective β sympathomimetic drugs; and
- 1.3 Selective β_2 sympathomimetic bronchodilator drugs.

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Drugs of group 1.1 exert both α and β sympathomimetic effects. They include the drug substances adrenaline and ephedrine. Both adrenaline and ephedrine are known clinically as bronchodilators. Though adrenaline, despite side effect induced via its α -sympathomimetic properties, is still used by some practitioners for the treatment of acute asthma, both adrenaline and ephedrine have been largely superseded in asthma therapy.

The drugs of group 1.2 have both β_1 and β_2 sympathomimetic activity but no, or only limited, α -sympathomimetic activity. Of the group 1.2 drugs, isoprenaline is the best known representative. Isoprenaline differs from the drugs of group 1.3 in its faster onset but shorter duration of action and its cardiac stimulating effects which result largely from its β_1 activity. Though isoprenaline has previously been extensively used as bronchodilator therapy in asthma, its use has today become clinically restricted. Thus, in the UK, a rise in the rate of asthma death in the 1960's believed to have been specifically associated with isoprenaline usage has resulted in discontinuation of its clinical application.

The selective β_2 sympathomimetic bronchodilator drugs of group 1.3 (herein referred to for convenience collectively as "GROUP 1.3 DRUGS") act, as their name implies, selectively on the β_2 adrenergic receptors. The GROUP 1.3 DRUGS include for example, the drug substances
a) TERBUTALINE, b) ALBUTEROL (also known as SALBUTAMOL),
c) FENOTEROL, d) HEXOPRENALEINE, e) RIMITEROL,
f) ISOETHARINE, g) METAPROTERENOL, h) REPROTEROL,
i) CLENBUTEROL, j) PROCATEROL, k) CARBUTEROL,
l) TULOBUTEROL, m) PIRBUTEROL, n) BITOLTEROL and, more recently, the so-called "long acting selective β_2 sympathomimetic bronchodilator drug substances"
o) FORMOTEROL, p) SAMBUTEROL and q) SALMETEROL
(R,S)-1-(4-hydroxy-3-hydroxymethylphenyl)-2-[6-(4-

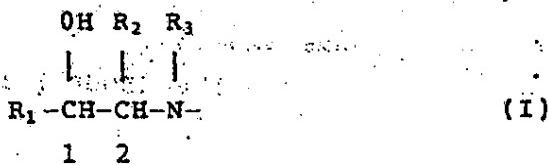
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-phenylbutoxy)hexylamino]ethanol]. All of the above recited GROUP 1.3 DRUGS are commercially available and clinically used, generally in pharmaceutically acceptable salt form, e.g. as the sulphate [(a), (b), (d) and (g)], hydrobromide [(c) and (e)], hydrochloride [(f), (h) to (l) and (p)], dihydrochloride [(d) and (m)], fumarate [(o)], methanesulfonate [(n)], hydroxynaphthoate [(q)] or, where appropriate, one or other of the hydrate forms thereof - see e.g. Merck Index, 11th edition (1989), items 9089 (a), 209 (b), 3927 (c), 4628 (d), 8223 (e), 5053 (f), 5836 (g), 8142 (h), 2347 (i), 7765 (j), 1840 (k), 9720 (l), 7461 (m), 1317 (n), 4159 (o) and 963 (p) and references cited therein and, for (q), Am. Rev. Resp. Dis. 137 (4; 2/2) 32 (1988).

Further GROUP 1.3 DRUGS currently in development include for example the drug substances r) BROXATEROL, s) ETANTEROL, t) IMOXITEROL, u) NAMINTEROL, v) PICUMETEROL, w) RP 58802 [Rhône-Poulenc], x) RU 42173 [Hoechst Roussel-Uclaf] and y) ZK 90055 [Schering].

GROUP 1.3 DRUGS characteristically contain as part of their structure an ethanolamine or 2-amino-ethanol moiety of formula I



in which R₁ is an aromatic group.

Commonly R₁ is 3,4- or 3,5-dihydroxyphenyl as in the case of the GROUP 1.3 DRUGS (a), (c), (d), (e), (f), (g) and (h) above or 4-hydroxy-3-hydroxymethylphenyl as in the case of the GROUP 1.3 DRUGS (b) and (q). R₁ may also be, e.g., 2-hydroxymethyl-3-hydroxy-6-pyridyl; 3,4-ditoluoyloxy-phenyl; 3-formylamino-4-hydroxyphenyl;

3,5-N,N-dimethylcarbamoyloxyphenyl; 4-amino-3,5-dichlorophenyl; 4-hydroxy-3-ureidophenyl; or 2-chlorophenyl as in the case of the GROUP 1.3 DRUGS (l), (m), (o), (p), (i), (x) and (l) respectively.

R_3 in formula I is commonly H. An exception in this respect is the GROUP 1.3 DRUG (e) above. In this case R_2 and R_3 together are a group of formula $-(CH_2)_4-$.

R_2 in formula I is also commonly H. Exceptions in this respect are the GROUP 1.3 DRUG (e); as noted above, as well as (f) and (j) in both of which R_2 is ethyl.

Since the formula I moiety comprises at least 1 asymmetric carbon atom (Cl in formula I), all of the GROUP 1.3 DRUGS exist in optically active isomeric form, with the said carbon atom having the (R) or (S) configuration [as designated using the Cahn-Ingold-Prelog system (Angew. Chem. Intern. Ed. 5, 385-415 (1966))]. When the said carbon atom is the sole asymmetric carbon atom present, GROUP 1.3 DRUGS thus exist as individual (R) or (S) enantiomers or in racemic [(RS)] form, i.e. as a 50:50 mixture of the (R) and (S) enantiomers.

Individual GROUP 1.3 DRUGS in which R_2 in the formula I moiety is other than H or in which the remainder of the molecule includes an asymmetric carbon atom exist in a variety of isomeric forms, i.e. in individual (R,R), (S,S), (R,S) and (S,R) isomeric form, as racemic [(RS,RS) and (RS,SR)] mixtures comprising the (R,R) plus (S,S) and (R,S) plus (S,R) enantiomeric pairs, as well as in the form of diastereomeric mixtures comprising all four isomeric forms. This is so, for example, in the case of the GROUP 1.3 DRUGS (c), (d), (e), (f) and (o) above.

Individual enantiomers [e.g. (R) or (S), or (R,R) or (S,S) enantiomers] of GROUP 1.3 DRUGS are known and have been

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described together with processes for their production in the literature. Pharmacological studies and clinical, e.g. metabolic, investigations employing healthy volunteers have also been carried out using individual enantiomers of GROUP 1.3 DRUGS. It is furthermore known that the β ,sympathomimetic/bronchodilator activity of GROUP 1.3 DRUGS resides primarily in individual enantiomers in which the hydroxy bearing carbon atom, C1 in formula I has the (R) configuration. The corresponding (S) enantiomer in contrast has no or very little bronchodilator activity. [See e.g. Murase et al., Chem. Pharm. Bull., 26 (4), 1123-1129 (1976); Hartley et al., J. Med. Chem. 14 (9), 895-896 (1971); Okamoto et al., J. Liq. Chromatogr. 11, 2147-2163 (1988), Koster et al., Biochem. Pharmacol. 35 (12), 1981-1985 (1986), Borgström et al., Br. J. Clin. Pharmac., 27, 49-56 (1989) and references therein.]

This knowledge notwithstanding, GROUP 1.3 DRUGS are marketed and employed for regular clinical usage, e.g. in the treatment of obstructive or inflammatory airways disease, in racemic [(RS)] form, that is as mixtures of the bronchodilatorily active (R) and inactive (S) enantiomeric pairs. [In the case of GROUP 1.3 DRUGS comprising two asymmetric carbon atoms the clinically employed racemic mixture is commonly that comprising the (R,R) plus (S,S) enantiomeric pair, i.e. the (RS,RS) racemate, as in the case of the so called "A racemate" of FENOTEROL - cf. Merck Index, Loc. cit.]

The GROUP 1.3 DRUGS can be administered orally, parenterally or (most commonly) by inhalation, e.g. using nebulisers or metered aerosol devices or as inhaled powders. Inhalation of GROUP 1.3 DRUGS presently represents the mainstay of bronchodilator therapy for the treatment of asthma of all grades of severity. The duration of bronchodilatation induced by the majority of GROUP 1.3 DRUGS is relatively short and they are employed to relieve asthma attack as and

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when it occurs. As indicated above, the more recently introduced GROUP 1.3 DRUGS, e.g. (o), (p) and (q) above, are characterised by their longer duration of action and hence apparent reduced frequency of dosaging required.

Although the GROUP 1.3 DRUGS are effective and generally seem to be well tolerated, their safety, especially at high dosages, has been questioned over many years and numerous reports have appeared on the adverse effects of GROUP 1.3 DRUG therapy (see e.g. Paterson et al: "American Review of Respiratory Disease", 120, 844 to 1187 (1979) especially at p.p. 1165 et seq.). More recently, from New Zealand, where a continuing increase in asthma death has been recorded, two case control studies reported in the Lancet have linked increase in asthma mortality to use of the GROUP 1.3 DRUG, FENOTEROL - see in particular Editorial "S₂ agonists in asthma: relief, prevention, morbidity", Lancet, 336, 1411-1412 (1990). A subsequently reported Canadian study finds that the use of inhaled GROUP 1.3 DRUGS, principally FENOTEROL and ALBUTEROL, is associated with "an increased risk of the combined outcome of fatal and near-fatal asthma, as well as of death from asthma alone" - see Spitzer et al., New England J. of Med., 326 (8), 501-506 (1992) and the Editorial to the same issue at page 560.

Various possible explanations for observed episodes of increased airway obstruction, arterial hypoxaemia or "anomalous" or "paradoxical" bronchospasm, as well as increased morbidity associated with GROUP 1.3 DRUG usage, in particular long term/high dose usage, have been proposed.

These have included, for example, reactive myogenic tone, increased inflammatory burden, adrenoceptor tachyphylaxis and induction of airway hyperreactivity, as well as the involvement of spasmogenic drug metabolic products or long term influence of aerosol spray propellants - see e.g. Paterson et al. loc. cit. and Morley et al. Eur. Respir. J.

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s, 1-5 (1990).

As already noted, an increase in asthma death had earlier been associated with use of the GROUP 1.2 DRUG isoprenaline. Isoprenaline is metabolised in part by the enzyme catechol-O-methyl transferase, giving a 3-methoxy derivative which has β -adrenoceptor antagonist activity. It has, for example, been suggested that it is this metabolite which was the cause of difficulty. More recently it has been proposed that isoprenaline-induced asthmatic exacerbation is due to an exacerbation of airways-hyperreactivity or inflammatory status common to the (S) [or (+)] and (R) [or (-)] enantiomers of isoprenaline [see e.g. : Mazzoni et al., Brit. J. Pharmacol, 91, 326 (1987); Morley et al., J. Physiol., 390, 180 P (1987) and Lancet, July 16, 1988, p. 160; and Sanjar et al., J. Physiol., 425, 43-54 (1990) — isoprenaline like the GROUP 1.3 DRUGS was employed clinically in (RS) racemic [or (\pm)] form.] No consensus on the subject has however been reached within the scientific community and no evidence has hitherto been adduced which might link experience with isoprenaline to that with GROUP 1.3 DRUGS.

At the same time there is mounting concern within the medical profession as to the potential dangers of GROUP 1.3 DRUG usage in asthma therapy. To quote the Lancet Editorial already referred to:

"These studies raise serious question about the use of β_2 agonists [i.e. GROUP 1.3 DRUGS]. The findings of Sears et al. could be interpreted as supporting the current trend towards earlier use of corticosteroids and other preventers of inflammation [for asthma therapy] rather than perseverance with an escalating bronchodilator regimen. The findings of the Nottingham and Dunedin groups also indicate that there is some way to go before long acting β_2 agonist preparations such as salmeterol and formoterol can be unreservedly recommended for routine use in the management

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of asthma. There seem to be clear advantages of compliance and possibly of anti-inflammatory activity associated with such agents, but the potential for adverse effects cannot be ignored. Clinicians researchers and pharmaceutical companies must now attempt to redefine the use of β_2 agonists in asthma." [Emphasis added.]

Equally there has been evident inability or reluctance to conceive of any problem in relation to GROUP 1.3 DRUG therapy as being inherent in GROUP 1.3 DRUGS themselves or as hitherto employed - cf. the following, taken from the Editorial to the New England Journal of Medicine also previously referred to: "Although ... too much reliance is placed on beta-agonists [GROUP 1.3 DRUGS], it is difficult to believe that the problem is related directly to the more regular use of inhaled beta-agonists."

In accordance with the present invention it has now been found that, whereas bronchodilator efficacy of GROUP 1.3 DRUGS is associated with, or associated primarily with, one optically active enantiomer, the bronchodilatory less active or inactive enantiomer or antipode induces an adverse effect, e.g. in asthma. (This finding does not, of course, exclude the possibility that the isomer having bronchodilator efficacy may also possess adverse pharmacological properties which are masked or compensated for by its beneficial bronchodilator efficacy.) The present invention thus surprisingly teaches that the long-standing problems inherent in GROUP 1.3 DRUG therapy may unexpectedly be met or ameliorated by the relatively simple expedient of administering GROUP 1.3 DRUGS not, as hitherto, in the form of a racemic mixture but in the form of the individual bronchodilatory effective enantiomer (referred to hereinafter for convenience as the "BRONCHODILATOR ENANTIOMER").

While the suitability, in particular of high-dose or

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long-term, GROUP 1.3 DRUG therapy has long been a subject of debate and, more recently, acute question, the practice of administering drugs of this group as racemic mixtures has continued. This practice has been accepted by drug registration authorities world-wide and even the most recently introduced of the GROUP 1.3 DRUGS have been developed for clinical use as racemic mixtures.

This practice is based upon the assumption or understanding that the non-bronchodilator component of the racemic mixture, i.e. the bronchodilatorily less or inactive enantiomer or antipode of the BRONCHODILATOR ENANTIOMER is devoid of any relevant drug effect and can thus be administered together with the BRONCHODILATOR ENANTIOMER essentially as inactive ballast and without risk to the patient. The teaching of the invention thus stands in stark opposition to long, widely established and continuing practice.

While simple in conception, the present invention thus runs contrary to the wisdom of the art. In that the GROUP 1.3 DRUGS clearly offer very considerable potential benefit for bronchodilator usage in asthma, the need to find a means of avoiding, ameliorating or restricting disadvantages inherent in their use is urgent and crucial. By meeting this need, the present invention may be anticipated to bring immeasurable benefit both to the medical profession and the world asthma population.

In accordance with the foregoing the present invention provides:

- A An improved (e.g. safer) method of treating inflammatory or obstructive airways disease or a method of treating inflammatory or obstructive airways disease with the avoidance, amelioration or restriction of deleterious side effect, in a human subject in need thereof, which

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method comprises administering to said subject a GROUP 1.3 DRUG, said GROUP 1.3 DRUG being administered predominantly in the form of its BRONCHODILATOR ENANTIOMER; or, in the alternative:

B A GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER for use in the improved (e.g. safer) treatment of inflammatory or obstructive airways disease in humans, or for use in the treatment of inflammatory or obstructive airways disease in humans to avoid, ameliorate or restrict deleterious side effect, or for use in the preparation of a pharmaceutical composition for use in such treatment.

GROUP 1.3 DRUGS to which the present invention applies include any selective β_2 sympathomimetic bronchodilator drug comprising an ethanalamine moiety, e.g. of formula I as illustrated above wherein R₁ is an aromatic group, for example a moiety of formula I as illustrated above wherein R₁, R₂ and R₃, individually or collectively have any one or more of the meanings hereinbefore recited.

Specific GROUP 1.3 DRUGS to which the present invention applies include any of the drug products (a) through (y), especially (a) through (q) hereinbefore identified and, in particular, (b) ALBUTEROL and the "long acting" GROUP 1.3 DRUGS, in particular (o) FORMOTEROL, (p) BAMBUTEROL and (q) SALMETEROL. The invention is to be understood as relating to GROUP 1.3 DRUGS both in free form as well as pharmaceutically acceptable acid addition salt form, e.g. as hereinbefore set forth for the GROUP 1.3 DRUGS (a) through (q), and including hydrate forms thereof. All references to GROUP 1.3 DRUGS, whether individually or collectively and in whatever manner, in relation to the present invention both herein and in the accompanying claims are to be understood accordingly as embracing such salt and hydrate forms.

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As hereinbefore described in relation to formula I, Cl in BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUGS characteristically has the (R) configuration. In the case of GROUP 1.3 DRUGS having a single asymmetric carbon atom BRONCHODILATOR ENANTIOMER will thus be the (R) enantiomer. In the case of GROUP 1.3 DRUGS having two asymmetric carbon atoms BRONCHODILATOR ENANTIOMER will be the (R,R) or (R,S) isomer. In practice, GROUP 1.3 DRUGS having two asymmetric carbon atoms have hitherto been used in clinic generally in the form of the (RS,RS) racemic mixture and it is the (R,R) enantiomer which generally has the greatest bronchodilator potency (see e.g. Murase et al., loc. cit.). In the case of GROUP 1.3 DRUGS having two asymmetric carbon atoms BRONCHODILATOR ENANTIOMER will thus usually be the (R,R) enantiomer.

In practicing the present invention, GROUP 1.3 DRUG is employed predominantly in the form of its BRONCHODILATOR ENANTIOMER. Preferably GROUP 1.3 DRUG will be employed in the form of its pure or substantially pure BRONCHODILATOR ENANTIOMER, that is in a form free or substantially free of other isomeric forms, in particular of the chirally opposite ("non-bronchodilator") antipode. Suitably GROUP 1.3 DRUGS will comprise at least >75%, preferably at least 90%, e.g. >95% or >98% BRONCHODILATOR ENANTIOMER. As previously indicated GROUP 1.3 DRUGS in pure or substantially pure isomeric form are known (see for example Murase et al. and Hartley et al. loc. cit. and other references referred to in the Merck Index hereinbefore cited) or may be obtained analogously, e.g. by resolution of diastereomeric salt forms/chromatographic techniques.

The present invention provides a method or use for the treatment of inflammatory airways disease, in particular for effecting bronchilatation, e.g. as a means of alleviating airways obstruction, in particular acute airways obstruction, e.g. asthma attack, occurring in such disease.

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the invention thus provides symptomatic, rather than prophylactic, therapy for such disease.

The teaching of the present invention is applicable in the therapy of inflammatory or obstructive airways disease, in particular any such disease for which GROUP 1.3 DRUG therapy is commonly practiced, for example chronic obstructive pulmonary disease, e.g. consequential to cystic fibrosis, emphysema and, especially, chronic bronchitis and, most especially, asthma.

The present invention avoids deleterious side effects hereinbefore resulting or observed in, e.g. asthmatic, patients consequent to conventional clinical usage of GROUP 1.3 DRUGS as racemic mixtures. In particular the invention provides means to avoid, ameliorate or restrict deleterious side effect, e.g. side effect deleterious to the airways. Thus the invention provides means to avoid, ameliorate or restrict exacerbation of disease status, for example basal disease, e.g. basal asthmatic, status or to avoid, ameliorate or restrict compromise or deterioration of lung function, or any other side effect concomitant to conventional clinical usage, for example "anomalous", "rebound" or "paradoxical" bronchospasm and, especially, increase in airway obstruction, exacerbation of late asthmatic response or non-specific bronchial reactivity or arterial hypoxaemia. Without limiting the present invention to any specific theory or mode of action, the present invention is in particular to be understood as providing a means for the avoidance, amelioration or restriction of exacerbation of airways hyperreactivity and/or of inflammatory or other event associated with, or which is an aetiological component of, inflammatory or obstructive airways disease, e.g. asthma. Such events are to be understood as including for example, inflammatory cell infiltration of the lungs or airways, connective tissue deposition or smooth muscle hyperplasia within the lungs or

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airways or other morphological change associated with asthmatic status. The present invention also provides a means of preventing or reducing morbidity, e.g. asthma morbidity, ascribable to conventional, e.g. high dosage or long term, GROUP 1.3 DRUG usage.

The present invention is especially applicable in the therapy of bronchial asthma of whatever type or genesis. It is applicable to both intrinsic and extrinsic asthma. It is especially applicable to the treatment of allergic or atopic (i.e. IgE-mediated) asthma or non-atopic asthma, as well as exercise induced asthma, occupational asthma, asthma induced following bacterial infection or drug, e.g. aspirin, ingestion and other non-allergic asthmas. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting chronic cough or wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", i.e. as embracing the treatment of "wheezy infant syndrome". Other diseases to which the present invention is in particular applicable include for example chronic obstructive pulmonary or airways disease (COPD or COAD).

As previously mentioned, the present invention embraces the understanding that BRONCHODILATOR ENANTIOMERS of GROUP 1.3 DRUGS may themselves exhibit adverse pharmacological properties in common with the non-bronchodilator antipodes, which are masked, or compensated for, by their bronchodilator efficacy. As a direct corollary to this and in the light of the understanding of said adverse effects as taught by the invention, the therapeutic benefit of BRONCHODILATOR ENANTIOMERS may be yet further improved by co-administration of drug substances capable of reversing or inhibiting the development of airways hyperreactivity, notably the drug substance KETOTIFEN (cf. Merck Index, loc. cit. item 5187). Accordingly in a further aspect the present invention provides:

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- C A method as defined under A above, which method additionally comprises administration of KETOTIFEN; or
- D A GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined under B above, wherein said use comprises use in conjunction with use of KETOTIFEN, i.e. additionally comprises administration of KETOTIFEN.

KETOTIFEN is known and commercially available, e.g. in pharmaceutically acceptable acid addition salt form, for example as its hydrogen fumarate, for use, inter alia, as an asthma prophylactic drug. References to KETOTIFEN herein are to be understood as embracing KETOTIFEN in free base form or in the form of any of its pharmaceutically acceptable acid addition salts.

For the above purposes KETOTIFEN will generally be administered in anti-asthmatically effective amount, i.e. at dosages conventionally administered for the prophylaxis of asthma, as hereinafter described. In practicing the invention KETOTIFEN may be administered either concomitantly with or independently of BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG, e.g. in a separate daily regimen during the course of therapy employing BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG.

The deleterious effects of the non-bronchodilator enantiomer (i.e. antipode of BRONCHODILATOR ENANTIOMER), of GROUP 1.3 DRUGS, e.g. of (S)-ALBUTEROL and (S)-TERBUTALINE [the dextro or (+) optically active isomers] as well as the advantages obtaining from the application of the present invention may be demonstrated in conventional animal models as well as in clinical trials for example as follows:

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Example 1: Influence of non-bronchodilator enantiomers of GROUP 1.3 DRUGS on airways hyperreactivity in the guinea pig

Guinea-pigs (circa 500g) are anaesthetised by intraperitoneal injection of sodium phenobarbitone (100mg/kg) and sodium pentobarbitone (30mg/kg) then paralysed by intramuscular injection of gallamine (10mg/kg). Animals are ventilated (8ml/kg, 1Hz) via a tracheal cannula using a mixture of air and oxygen (50:50, v/v). Ventilation is monitored at the trachea by a pneumotachograph (type 0000; Fleisch, Zabona A.G., CH) connected to a differential pressure transducer (type MP 4514871, Validyne, USA). Coincident pressure changes within the thorax are measured via an intrathoracic cannula, using a differential pressure transducer (type MP 4524, Validyne, USA); blood pressure and heart rate are recorded from the carotid artery using a pressure transducer (type P23Dd, Gould, USA). From measurements of air-flow and intrathoracic pressure, both airway resistance (R_L) and compliance (C_{dyn}) are calculated at each respiratory cycle using a digital electronic pulmonary monitoring system (PMS, Mumed Ltd, London, UK) and recorded. Blood pressure, intrathoracic pressure, airflow and computed R_L and C_{dyn} in real time are displayed on a visual display unit (model AT3, IBM, USA). Experimental data is stored electronically and experimental traces or processed data are plotted on a laser printer (Laser Jet Series II, Hewlett Packard, USA) as required.

- 1) In a first series of experiments responsiveness of the airways to intravenous injection of histamine (0.56-1.8 μ g/kg at 10 min. intervals) is defined before, and twenty minutes after, intravenous infusion of (S)-ALBUTEROL over one hour (total dose 100 μ g/kg). Increase of airway resistance following intravenous injection of histamine (0.56, 1.0 & 1.8 μ g/kg) in one experimental run is recorded as (10 \pm 1.8, 41.03 \pm 9.14 & 223 \pm 69.91 cmH₂O/l/sec.) before and (60.01 \pm 12.86, 149.06 \pm 31.64

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& 539 ± 185.14 cmH₂O/l/sec.) after infusion of (S)-ALBUTEROL (100 μ g/kg). Incremental differences for successive doses of histamine recorded are 50.1, 108.03 & 316 cmH₂O/l/sec. By comparison, increased airway resistance in response to intravenous injection of histamine (0.56, 1.0 & 1.8 μ g/kg) before and after intravenous infusion of vehicle (0.9% saline) is recorded as (7.05 ± 1.17, 21.68 ± 3.05, 86.45 ± 14.13 and 15.04 ± 2.57, 30.42 ± 5.39, 101 ± 20 respectively) so that incremental differences for successive doses of histamine are 7.99, 8.74 & 14.75 cmH₂O/l/sec.

- 2) In a second series of experiments employing guinea pigs actively sensitised to ovalbumin [as described in Sanjar et al., Br. J. Pharmacol. 99, 679-686 (1990)], responsiveness of the airways to intravenous injection of histamine [as under 1 above] before and after intratracheal instillation of tragan (0.2ml) alone or containing (S)-ALBUTEROL (10 μ g) or (S)-TERBUTALINE (10 μ g) is defined. In this test model both (S)-ALBUTEROL and (S)-TERBUTALINE are found to induce significant increase of airway resistance on intravenous injection of histamine as compared with animals receiving tragan only.

Similar or equivalent results are obtained employing non-bronchodilator enantiomer of other GROUP 1.3 DRUGS, e.g. the (S) or (S,S) enantiomer of GROUP 1.3 DRUGS (c) to (q) as hereinbefore set forth, at the same or equivalent dosage rates.

Example 2: Influence of non-bronchodilator enantiomer of GROUP 1.3 DRUGS on the lung function of asthmatic patients

The trial is carried out in double blind, placebo controlled format. Subjects are stable asthmatics with evident on-going

compromisation of lung function. Typical subjects include allergic asthmatics or non-allergic (intrinsic asthmatics) with no evidence of atopy, clinically stable and using conventional nebulised GROUP 1.3 DRUGS therapy regularly. Asthma medication is withdrawn ca. 12 hours prior to investigation and pulmonary function (FEV₁) is monitored at regular intervals prior to and following administration of test substance or placebo (vehicle). Additionally PD20 for histamine is determined by measuring the effect of inhaled aerosols of histamine solutions (0.0625-8mg/ml) 0.5 hrs before as well as 2.5 and 7.5 hrs after exposure to test substance/vehicle.

Test substance comprises GROUP 1.3 DRUG administered by the inhaled route either in racemic form (in accordance with conventional practice) at conventional single dose level or in substantially pure non-bronchodilator enantiomeric form at 0.25 to 0.5 x the conventional single dose level.

In subjects receiving GROUP 1.3 DRUG in conventional, racemic form, e.g. receiving (R,S)-ALBUTEROL, (R,S)-TERBUTALINE or (RS,RS)-FENOTEROL, dose related reduction of airflow obstruction is observed as compared with subjects receiving placebo. Results thus accord with conventional observations for GROUP 1.3 DRUG therapy.

In subjects receiving GROUP 1.3 DRUG in substantially pure non-bronchodilator enantiomeric form, e.g. receiving (S)-ALBUTEROL, (S)-TERBUTALINE or (S,S)-FENOTEROL, after potential transient reduction in airflow obstruction attributable to any BRONCHODILATOR ENANTIOMER present in the administered material, individual subjects exhibit a sustained fall in FEV₁, accompanied by increased wheezing and discomfort as compared with results obtained from subjects receiving placebo.

In practicing the present invention, BRONCHODILATOR

ENANTIOMER of GROUP 1.3 DRUG may be administered in any form or by any route known or conventionally employed in relation to use of selected GROUP 1.3 DRUG in conventional racemic form, e.g. orally in the form of tablets, capsules, syrups, granulates and micro-granulates etc., intravenously in the form of an injectable solution, or by the pulmonary route. Preferably BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG will be administered via the pulmonary route, e.g. by inhalation from an appropriate dispenser device, e.g. as hereinbefore indicated or as otherwise known or used in the art.

Dosages of BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG employed in practicing the present invention will vary, e.g. depending on the particular GROUP 1.3 DRUG selected, the selected route of administration, the particular condition to be treated, the severity of the condition to be treated and the effect desired. In general however dosages of BRONCHODILATOR ENANTIOMER of the selected GROUP 1.3 DRUG will be of the order of about 40% to 60%, e.g. about 50%, of dosages administered employing the same GROUP 1.3 DRUG in conventional, racemic form. This lowering of the dosage may readily be achieved, e.g. by preparing galenic forms comprising BRONCHODILATOR ENANTIOMER of the selected GROUP 1.3 DRUG as active ingredient in the same concentration as in conventionally employed dosage forms and reducing the daily dosaging requirement by ca. 50%, or by preparing galenic forms comprising BRONCHODILATOR ENANTIOMER as active ingredient at ca. 50% of the concentration conventionally employed for GROUP 1.3 DRUG and maintaining conventional daily dosaging requirements. In the latter case, the 50% reduction in active ingredient content will be compensated by the addition of the equivalent amount of an appropriate, inert pharmaceutically acceptable diluent or carrier.

Thus for administration by inhalation, (R,S)-ALBUTEROL is conventionally administered, e.g. via a metered dose aerosol delivering 100 μ g racemic drug substance per actuation. For

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adults, administration is conventionally effected 3 to 4 times/day with 2 actuations at each administration, to give a dosage per administration of 200 μ g drug substance. The canisters employed in the delivery device contain ca. 20mg (R,S)-ALBUTEROL or sufficient for 200 actuations.

Employing pure or substantially pure (R)-ALBUTEROL in accordance with the present invention, administration can be effected employing an identical regimen to that used for the racemate but using canisters containing ca. 10mg (R)-ALBUTEROL, giving a metered dose of 50 μ g drug substance per actuation or a dosage of 100 μ g drug substance 3 to 4 times/day, or using canisters containing ca. 20mg (R)-ALBUTEROL, giving a metered dose of 100 μ g drug substance per actuation and applying only 1 instead of 2 actuations at each administration.

From the foregoing it will be appreciated that suitable galenic formulations for practicing the present invention may be in all material respects identical to those employed for delivery of conventional, racemic GROUP 1.3 DRUG, but with appropriate compensation for reduction in active ingredient content where required.

As previously indicated, in practicing the present invention, BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG is preferably administered by the pulmonary route, e.g. by inhalation. Compositions employed will thus preferably be in a form permitting, enabling or adapted for administration via the pulmonary route. Such forms will in particular include free flowing, or freely flowable, dispersible forms, for example liquid or finely divided powder forms, capable of or adapted to delivery as an inhalable spray, mist or dispersion in air, e.g. following delivery from an appropriate, e.g. aerosol, atomiser, dry powder dispenser or like device. Carriers, excipients, diluents etc. employed in such compositions will likewise preferably be selected from

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amongst those known, employed and/or recognised as suitable for pulmonary administration.

The following examples are illustrative of compositions suitable for use in accordance with the present invention:

Example 3

3.1 Tablets or capsules may contain the active agent in admixture with conventional pharmaceutically acceptable excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose and talc, granulating and disintegrating agents, e.g. starch and alginic acid, flavouring, colouring and sweetening agents, binding agents, e.g. starch, gelatin and acacia, and lubricating agents, e.g. magnesium stearate, stearic acid and talc, e.g. as follows:

INGREDIENTS	WT./DOSE
(R)-METAPROTERENOL (as its sulfate) in substantially pure form	20.00 mg
Lactose (200 mesh)	90.00 mg
Corn starch	35.00 mg
Silicon dioxide (Aerosil 200)	1.75 mg
Magnesium stearate	<u>3.25 mg</u>
TOTAL	150.00 mg

The ingredients are intimately admixed employing conventional galenic procedures, filled into hard gelatin capsules and the capsules sealed.

The capsules are useful in accordance with the present invention in the therapy of asthma on administration in adults 2x daily to give a daily dose of 40mg/day/p.o.. Alternatively capsules may be prepared comprising 10.00mg

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(R)-ORCIPRENALE (as its sulfate) for administration in adults 4x daily.

Equivalent oral compositions may be prepared comprising BRONCHODILATOR ENANTIOMER of any other GROUP 1.3 DRUG, e.g. as hereinbefore referred to, either at conventional unit dosage drug concentration* for administration at 50% conventional dosaging rate* or at 50% conventional unit dosage drug concentration for administration at conventional dosaging rate.

[*For the drug substances TERBUTALINE, FENOTEROL and CARBUTEROL for example, conventional oral unit dosage forms (comprising racemic material) comprise 2.5 or 5.0mg; 5.0 or 10.0mg; and 2.3mg racemic material respectively, for administration 2 to 4x daily.]

3.2. Inhalable aqueous solutions may also be prepared in conventional manner, e.g. optionally with the addition of ethanol as solubilizer, and with acid buffering agents to an end pH of 4.0. Stabilizing and preserving agents may also optionally be added. Suitable compositions for pulmonary application from a conventional metered delivery device may be made up for example as follows:

Aqueous solutions are prepared comprising (a) 0.5, (b) 1.0 or (c) 2.0 mg (R)-ALBUTEROL as the sulphate/ml and adjusted to pH ca. 4.0 by the addition of H₂SO₄. Compositions are filled in 2.5ml amounts, comprising 0.5%, 1.0% and 2.0% (R)-ALBUTEROL, into plastic ampoules for insertion into a conventional metered device, e.g. for use, in relation to composition (a) with 2x actuation delivering a total of 100μg (R)-ALBUTEROL 2 to 4x daily, in relation to composition (b) with 1x actuation delivering a total of 100μg (R)-ALBUTEROL 2 to 4x daily or in relation to composition (c) with 1x actuation delivering a total of 200μg (R)-ALBUTEROL 1 to 2x daily.

Equivalent compositions may be prepared comprising BRONCHODILATOR ENANTIOMER of any other GROUP 1.3 DRUG, e.g. as hereinbefore referred to, either at conventional unit drug concentration** for administration at 50% conventional dosaging rate or at 50% conventional drug concentration for administration at conventional dosaging rate.

[**For the drug substances ISOETHARINE, METAPROTERENOL, TERBUTALINE, FENOTEROL and CARBUTEROL for example, conventional inhaled doses (per puff) are 350 μ g; 650 μ g; 250 μ g; 200 μ g; and 100 μ g racemate respectively, for use in two puffs generally administered 2 to 4 or up to 6x daily.]

In accordance with the foregoing the present invention also provides:

- E A pharmaceutical composition comprising a GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER as active ingredient, together with a pharmaceutically acceptable diluent or carrier therefor.

Pharmaceutical compositions are to be understood as being, in particular, compositions of which the individual components are not only suitable or allowable for therapeutic usage but which are manufactured and processed under conditions of sterility appropriate or required for therapeutic usage.

When the method of the present invention is practiced in conjunction KETOTIFEN therapy, dosages of KETOTIFEN employed will generally be the same or of similar order to KETOTIFEN dosages as conventionally employed for the prophylaxis or management of asthma, that is of the order of 1 to 4mg, preferably 2 or 4mg/day/p.o., suitably administered in 1 or 2mg doses, preferably 1x or 2x daily, or in liquid e.g. syrup form. Suitable oral dosage forms, e.g. 1mg and 2mg

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tablets and capsules as well as syrup formulations comprising KETOTIFEN as active ingredient, for use in practicing the present invention are known and commercially available.

Utility of the present invention may also be demonstrated in clinical trials, for example, performed as follows:

CLINICAL TRIAL I

Trial subjects are selected from patients having a clinical history of asthma and demonstrable airway obstruction (e.g., FEV₁ less than predicted from standard tables) that is resolved by inhalation of clinical doses of GROUP 1.3 DRUGS in conventional, racemic form [e.g. of (R,S)-ALBUTEROL]. Subjects also exhibit demonstrable increase in airway reactivity to inhaled histamine or methacholine. Typically, selected subjects are young adults (ca. 15 to 25 years of age) allergic to pollens, animal danders or house dust mite, using inhaled conventional, racemic GROUP 1.3 DRUG therapy intermittently (e.g. according to subjective perception of symptoms), with or without additional anti-asthma therapy such as inhaled steroid, cromoglycate or KETOTIFEN.

Trial subjects are divided into separate groups receiving either conventional, racemic GROUP 1.3 DRUG [e.g. (R,S)-ALBUTEROL] at conventional doses of 200 μ g or BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG dosing [e.g. (R)-ALBUTEROL] at 50% doses of 100 μ g, all doses administered by inhalation regularly, e.g. 2 to 4x daily over a period of 1 to 6 months. Concomitant additional therapy, as mentioned above is maintained where used. Subjects are monitored at monthly intervals during the course of the trial period for airways hyperreactivity, preferably using leukotriene C₄ or E₄ as test spasmogen, e.g. as reported in references already referred to hereinbefore.

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Increase in airway hyperreactivity is evidenced in subjects receiving conventional, racemic GROUP 1.3 DRUG. Subjects receiving BRONCHODILATOR ENANTIOMER in contrast exhibit a clearly restricted tendency to increase in hyperreactivity but exhibit equivalent benefit in terms of bronchodilator action during exacerbation. In subjects receiving concomitant KETOTIFEN yet further restricted trend towards increase in hyperreactivity is observed.

CLINICAL TRIAL II.

Subjects are selected from patient groups as described for TRIAL I. Subjects receive conventional, racemic GROUP 1.3 DRUG [e.g. (R,S) ALBUTEROL at 200 μ g by inhalation] or BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG [e.g. (R)-ALBUTEROL at 100 μ g by inhalation]. The alternative therapies are assigned to individual subjects in randomized, double-blind manner. Pulmonary function (e.g. FEV₁) and sensitivity to a test of airway hyperreactivity (e.g. inhaled aerosolised histamine) is determined before drug-administration and after intervals (e.g. of 2 and 5 hours) post drug-administration.

In the case of subjects receiving conventional, racemic GROUP 1.3 DRUG, evident mismatch is recorded between observed drug bronchodilator efficacy and suppression of manifestation of hyperreactivity, such that there is no observed protection from manifestation of hyperreactivity even though substantial bronchodilator response remains evident. In subjects receiving BRONCHODILATOR ENANTIOMER, degree of mismatch is significantly reduced while bronchodilator efficacy is maintained.

CLAIMS

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1. A selective β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use in the improved treatment of inflammatory or obstructive airways disease in humans.
2. A selective β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in claim 1, wherein the improved treatment comprises treatment to avoid, ameliorate or restrict occurrence of side effect deleterious to the airways.
3. A selective β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in claim 1, wherein the improved treatment comprises treatment to avoid, ameliorate or restrict exacerbation of basal disease status or compromise or deterioration of lung function.
4. A selective β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in any one of claims 1 to 3, wherein said use comprises use in conjunction with use of Ketotifen.
5. The BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimetic bronchodilator drug in pure or substantially pure form for use as defined in any one of claims 1 to 4.
6. The use of a selective β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER or the use of the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimetic bronchodilator drug in pure or substantially pure form for the preparation of a pharmaceutical composition for use in a method of

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treatment as defined in any one of claims 1 to 4.

7. A selective β_2 sympathomimetic bronchodilator drug selected from the group consisting of terbutaline, albuterol, fenoterol, hexoprenaline, rimiterol, isoetharine, orciprenaline, reprotoxol, clenbuterol, procaterol, carbuterol, tolbuterol, pributetol, bitolterol, formoterol, bambuterol and salmeterol predominantly in the form of its BRONCHODILATOR ENANTIOMER or the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimetic bronchodilator drug selected from the aforesaid group in pure or substantially pure form for use as defined in any one of claims 1 to 4 or 6.
8. A pharmaceutical composition comprising a β_2 sympathomimetic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER or the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimetic bronchodilator drug in pure or substantially pure form together with a pharmaceutically acceptable diluent or carrier therefor.
9. A pharmaceutical composition according to claim 8 wherein the β_2 sympathomimetic bronchodilator drug is selected from the group defined in claim 7.
10. Ketotifen for use in the preparation of a pharmaceutical composition for use in further improving use as defined in any one of claims 1 to 3 of a selective β_2 sympathomimetic bronchodilator drug in the form of its BRONCHODILATOR ENANTIOMER or of the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimetic bronchodilator drug in pure or substantially pure form.



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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: BN Corporation, LLC

Application No./Patent No.: 5,477,735 Filed/Issue Date: December 26, 1995

Entitled: Two-Wire Constant Current Transducer

BN Corporation, LLC, a Delaware limited liability company

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. the assignee of the entire right, title, and interest; or
 2. an assignee of less than the entire right, title and interest.

The extent (by percentage) of its ownership interest is _____%
 in the patent application/patent identified above by virtue of either:

A. An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 6660, Frame 0752, or for which a copy thereof is attached.

OR

B. A chain of title from the inventor(s) of the patent application/patent identified above, to the current assignee as shown below:

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Additional documents in the chain of title are listed on a supplemental sheet.

Copies of assignments or other documents in the chain of title are attached.

[NOTE: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

June 7, 2002

Tara A. Pilipon

Date

Typed or printed name

Signature

Secretary

Title

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